UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/508,967	04/07/2000	MATS WAHLGREN	45300-59676	4801

466 7590 05/18/2005

YOUNG & THOMPSON
745 SOUTH 23RD STREET
2ND FLOOR
ARLINGTON, VA 22202

EXAMINER	
MINNIFIELD, NITA M	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 05/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/508,967	WAHLGREN ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39,42-46,48 and 52-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *53 and 54* is/are allowed.

6)☒ Claim(s) *39,42-46,48,52,55 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892) 5 sheets

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

S-O-O

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 22, 2005 has been entered.

2. Applicants' amendment after final filed December 7, 2004 is acknowledged and has been entered. Claims 1-38, 40, 41, 47, and 49-51 have been canceled. Claims 39, 44-46 and 48 have been amended. New claims 52-56 have been added. Claims 39, 42-46, 48 and 52-56 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment and/or comments, with the exception of those discussed below.

3. Claims 43, 45 and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a pharmaceutical composition comprising an isolated polypeptide originating from a malaria erythrocyte membrane protein of the sequence according to amino acids 1-415 of SEQ ID NO: 1 and a pharmaceutically acceptable carrier (see claim 43), or a composition comprising an

isolated polypeptide originating from a malaria erythrocyte membrane protein of the sequence according to amino acids 79-415 of SEQ ID NO: 1 and a pharmaceutically acceptable carrier (see claims 45 and 48).

Figure 2C of the application discloses the amino acids 1-415 of SEQ ID NO: 1 and amino acids 79-415 of SEQ ID NO: 1. The examples set forth in the specification use the entire isolated polypeptide originating from a malaria erythrocyte membrane protein of the sequence according to SEQ ID NO: 1, which is the PfEMP1. The specification teaches the identification of a polypeptide termed PfEMP1, which is useful as a receptor for malaria erythrocyte membrane protein.

However, the specification is not enabled for pharmaceutical compositions comprising something less than the entire polypeptide, that is amino acids 1-415 or amino acids 79-415 of SEQ ID NO: 1. The specification fails to teach how the fragment of the polypeptide, amino acids 1-415 or amino acids 79-415 of SEQ ID NO: 1, was used in a pharmaceutical composition. Further, the claims recite a pharmaceutical composition (or a composition comprising the polypeptide and a pharmaceutically acceptable carrier, which would be a pharmaceutical composition) however, it is not clear what its particular use is. The Examiner interprets that the composition will be used to treat malaria or as a vaccine to protect against malaria in view of the need for a more protective vaccine as asserted in the prior art. When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that use. See MPEP 2164.01(c). The specification is not enabled for the pharmaceutical compositions as presently claimed.

The claimed invention appears to indicate a pharmaceutical use (i.e. vaccine) for the claimed composition. However, the specification has not enabled such a composition. The specification has described at pages 14 and 20-22 a pharmaceutical composition but no actual enablement for using the claimed polypeptide has been set forth. The specification contemplates administration for prophylactic and/or therapeutic treatment as well as preventing. The specification must teach how to make the claimed composition without undue experimentation and must teach how to use the composition for at least one pharmaceutical use without undue experimentation. It is noted that a pharmaceutical composition should have some pharmaceutical use; use as a drug or therapeutic agent. A therapeutic agent is considered any substance, other than food, used in the prevention, diagnosis, alleviation, treatment, or cure of disease in man and animal. A drug is defined as an agent intended for use in the diagnosis, mitigation, treatment, cure, or prevention of disease in humans or in other animals. One of the most astounding qualities of drugs is the diversity of their actions and effects on the body.

There are no animal models to show that the polypeptide indeed treated infection in patients. The development of vaccine and treatment therapies for individuals infected with malaria has been hampered by the fact that there is still no vaccine to prevent malaria. Baruch et al point out (WO 96/33736) that antibodies raised against a particular parasite will only react by parasitized erythrocyte (PE) agglutination with PE from the same strain (page 3). Studies have also shown that the malaria parasite exhibits variant surface antigens in different geographical locations hampering effective development of vaccine and treat therapies.

The art is replete with studies that show that at present there is no vaccine or composition to protect against malaria. The state of the art indicates that at present there are no vaccines that protect against malaria. Arevalo-Herrera et al indicates that because of the complexity of the parasite's life cycle the development of a universal, effective and long lasting vaccine is difficult (p. 444). Arevalo-Herrera et al states that since the use of whole malaria parasites as vaccines is not feasible, parasite sub-unit vaccines are being envisaged either making use of recombinant technology, peptide synthesis or naked DNA injection. Even though it is accepted that malaria vaccines need to simultaneously target the different parasite developmental stages, most vaccine trials concentrate on individual parasite targets, especially from *P. falciparum*. The use of a multi-stage and multi-species vaccine is expected to be advantageous because of simultaneous priming of synergistic immune mechanisms targeting the main parasite species circulating in a given region. (p. 444, col. 2) Arevalo-Herrera et al indicates that even though most efforts towards vaccine development have been focused on *P. falciparum*, development of a worldwide efficient malaria vaccine will require the inclusion of components from two prevalent malaria species, *P. falciparum* and *P. vivax* at least (p. 444, col. 2).

Smith et al teaches that analysis of the PfEMP1 sequence provides insight into domain function and protein architecture with potential implication for malaria disease (abstract). "An exciting possibility is that the sequence approach might provide insights into cytoadherence and *P. falciparum* pathogenesis. For instance, ICAM-1 and CSA have been linked to cerebral and placental malaria, respectively. Do other PfEMP1 proteins that adhere to ICAM or CSA use DBLβ-C2 and DBLγ domain? This is an important consideration for vaccine design, especially if the

different DBL sequence types have slightly different structures." (p. 541, col. 2) Smith et al also teaches that their studies will provide insights to focus vaccine directed immunity on conserved and critical PfEMP1 sites, and that the sequence approach provides insight into PfEMP1 structure and function with potentially significant implications for malaria disease and vaccine and therapeutic interventions; not that these compositions have been developed (p. 544, cols. 1 and 2). Bouharoun-Tayoun et al 2004 states that the study of parasite antigens targeted by ADCI effector antibodies has led to the characterization of MSP-3, a 48 kDa protein present on the surface of the *P. falciparum* merozoite. Cytophilic antibody response against MSP-3 is highly correlated with protective immunity. MSP-3 is currently used as a candidate malaria vaccine in clinical trials (p. 2, col. 1). The art indicates that it is a vaccine candidate but to date no vaccine against malaria using MSP-3, the whole protein or portions of the protein, has been disclosed.

Further, the art teaches problems with other proteins from Plasmodium as vaccine components. Kurtis et al 2001 states that a vaccine is urgently needed to stem the global resurgence of *P. falciparum* malaria; LSA-1 is one of a few proteins known to be expressed by liver-stage parasites, holds particular promise as a vaccine (abstract). Kurtis et al 2001 states that despite "important advances, such as the circumsporozoite protein (CSP)-based vaccine called RTS, S, the goal of a safe and broadly effective malaria vaccine remains unfulfilled. The parasite's complex life-cycle offers several targets for intervention in the human host and the mosquito vector and vaccines against sporozoite, intrahepatic, blood and sexual stages of the parasite are currently in development." (p. 219, col. 1). As of 2001, there is no effective vaccine that comprises the LSA either alone or in combination with other malaria proteins. Further, because LSA is a liver specific antigen,

investigation of its immunological significance is restricted to human studies because no homologue in mouse or non-human primate malarias has been identified (p. 219, col. 1). Others such as Taylor-Robinson et al 2001 have also indicated that LSA-1 may be a good candidate for a vaccine, but no vaccine has been produced that has been shown to be effective (see also Moorthy et al 2004; Ballou et al 2004; Joshi et al 2000; Kurtis et al 1999; Cox 1992; Ntumngia et al 2004; Stowers et al 2001). Shi et al, 1999 indicate that a multicomponent, multistage malaria vaccine can induce immune responses that inhibit parasite development at multiple stages. The rationale and approach used in the development of a multicomponent *P. falciparum* vaccine will be useful in the development of a multispecies human malaria vaccine and vaccines against other infectious diseases (see abstract). "Although studies of immunogenicity and the results of *in vitro* protection experiments have been promising for many of the single stage-specific vaccine candidate antigens, the test of *in vivo* protection has not always been satisfactory. There is consensus, however, that a highly effective malaria vaccine would require a combination of key antigens and/or epitopes from different stages of the life cycle and that induction of both humoral and cellular immunity is required for optimal efficacy. Such a multicomponent malaria vaccine would also circumvent the problems associated with host genetic restriction and antigenic variability in the case of single antigen-based vaccines." (Shi et al, 1999, p. 1615, paragraph bridging cols. 1-2). Shi et al 1999 also indicates that multiple protective immune responses against multiple antigens from different stages will be needed to protect against malaria (p. 1618, col. 2). "Although a single-antigen and/or stage-specific vaccine could provide protection against infections, there are several reasons to advocate a multivalent, multistage malaria vaccine. A major

concern with a single antigen-based vaccine is that an antigenic variant population of the parasite not recognized by the vaccine will cause infection (with heterologous parasites) and cause disease." (see p. 1618-1619).

In view of the fact that the specification does not set forth any enablement with regard to direction or guidance and the absence of working examples for the claimed pharmaceutical composition (that could be used as a vaccine or in therapy), and the fact that the state of the art teaches that there are no single antigen or stage specific vaccines against malaria and the unpredictability and difficulty in obtaining an effective pharmaceutical compositions directed against malaria comprising the claimed isolated polypeptide there would be undue experimentation necessary for a person of skill in the art to practice the claimed invention. For the reasons set forth above, the pharmaceutical compositions as claimed are not enabled.

Applicants have, in the December 7, 2004 amendment, reminded the Examiner that it is a well-founded principle and matter of law that any assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubt so expressed. Indeed, as a matter of law, the expressed teaching of a patent specification cannot be controverted by mere speculation and unsupported assertions on the part of the Patent Office. As to the present application, applicants do disclaim any of the previously recited utilities for the claimed composition. However, claims 43, 44, 45 and 48 have been amended to generically recite a composition. As the Examiner is aware, MPEP 2164.01(c) that when a compound recited use, any enabled use that would reasonably correlate with provides

composition claim is not limited by the entire scope of that claim is sufficient to preclude a rejection for nonenablement. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently, supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.

However, it is noted that the rejection above sets forth evidence to support the assertions set forth in the 112, first paragraph rejection (see pages 3-8 of this Office Action). Further, it is noted that the rejection is not based on a scope of enablement, but rather a lack of enablement of a pharmaceutical composition comprising amino acids 1-415 of SEQ ID NO: 1 or amino acids 79-415 of SEQ ID NO: 1 and a pharmaceutically acceptable carrier. The specification does not indicate that this portion of the PfEMP1 can function to treat or prevent malaria, as would be the use with a pharmaceutical composition that comprises polypeptides comprising amino acids 1-415 of SEQ ID NO: 1 or amino acids 79-415 of SEQ ID NO: 1 The cited references indicate the state of the art regarding malaria. It is also noted that the rejected claims, 43, 45 and 48, are directed to a pharmaceutical composition, not a generic composition as asserted by Applicants. The rejection is maintained for the reasons of record.

4. The rejection of claims 39, 42-46, 48, 52, 55 and 56 under 35 U.S.C. § 102(b) as anticipated by Helmby et al, 1993 (Infection and Immunity, 61/1284-288) is maintained. This rejection is maintained for essentially the same reasons as set forth in the last Office action.

Helmby et al teach the isolation of a 28 kD erythrocyte protein from *Plasmodium falciparum* malaria parasite (page 285). The protein was administered to rabbits in an effort to produce antibodies. The 28 kD protein is the same as the claimed protein. Characteristics such as amino terminal part, the number of amino acids as well as the binding capability would be inherent in the protein of the prior art. The claims are directed to an isolated polypeptide originating from a malaria erythrocyte membrane protein of the sequence according to amino acids 1-415 of SEQ ID NO: 1 or amino acids 79-415 of SEQ ID NO: 1. The specification indicates that the molecular weight of SEQ ID NO: 1 is 260 kD and has 2228 amino acids. The specifically claimed portion of SEQ ID NO: 1 would appear to have a much smaller molecular weight as is indicated in Helmby et al.

Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

It should be noted that the recitation of "pharmaceutical" is being viewed as intended use. Additionally, Applicant's use of the open-ended term "comprising" in the claims fails to exclude unrecited ingredients and leaves the claims open for inclusion of unspecified ingredients, even in major amounts. See In re Horvitz, 168 F 2d 522, 78 U.S.P.Q. 79 (C.C.P.A. 1948) and Ex parte Davis et al., 80 U.S.P.Q. 448 (PTO d. App. 1948).

The rejection is maintained for the reasons of record. Applicants' arguments filed December 7, 2004 have been fully considered but they are not deemed to be persuasive. Applicants have asserted that the isolated small protein of Helmby et al is a rosettin, which are surface antigens on *P. falciparum* infected red blood cells. Applicants again refer to Fernandez et al. However, the protein is a surface protein on the surface of live infected erythrocytes (p. 284) the same as Applicants. Applicants have asserted that the polypeptides have a molecular size of less than 200 kD and that this is a size quite distinct from the known PfEMP1 antigens. However, the molecular weight of the polypeptide is not recited in the claims. Further, the claims recite an isolated polypeptide originating from a malaria erythrocyte membrane protein of the sequence according to amino acids 1-415 of SEQ ID NO: 1 or amino acids 79-415 of SEQ ID NO: 1, which appear to be less than 200 kD. None of the claims recite the molecular weight. Further, the claims do not set forth how the molecular weight was determined and the claims recite that the polypeptide "comprises" therefore it is not clear what the polypeptide contains. With regard to the molecular weight, since the method of molecular weight determination has not been set fort, it would appear that the prior art discloses the same polypeptide. Similar molecular weights are disclosed in the prior art. Therefore, Helmby et al would appear to disclose the claimed invention.

5. Claims 53 and 54 are allowable.

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM
May 10, 2005